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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,540	09/27/2000	Timothy W. King	121117-1000	6703

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EXAMINER	
PULLIAM, AMY E	
ART UNIT	**PAPER NUMBER**
1615	12

DATE MAILED: 10/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/671,540	Applicant(s) KING ET AL.	
	Examiner Amy E Pulliam	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3\ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,23-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 23-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of Papers

Receipt is acknowledged of the Response, received by the Office on August 8, 2002.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 13, 14, 16-18, and 23-36 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,643,605 to Cleland *et al.*. Cleland *et al.* disclose methods and compositions for the encapsulation of adjuvants in PLGA microspheres (abstract). First, Cleland *et al.* teach that encapsulation is a method for formulating an active agent into a composition useful for controlled release of the active agent. More specifically, Cleland *et al.* teach the PLGA is first dissolved in an organic solvent, such as methylene chloride. A concentrated antigen or adjuvant solution, or dry antigen or adjuvant is added to the polymer solution. An emulsification bath of polyvinyl alcohol is added, followed by a hardening bath to create microspheres, followed by mixing at a high speed. The microspheres can then be dried by methods such as lyophilization, vacuum drying, and fluidized bed drying (c 7, l 58 – c 8, l 33). Additionally, Cleland *et al.* teach the inclusion of additives such as polyethylene glycol (c 9, l 26) and other excipients such as buffers and chelating agents (c 9, l 54-55).

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant argues that Cleland addresses the encapsulation of an adjuvant and antigen, whereas the present invention relates to the use of microspheres as delivery vehicles for bioactive substances. Applicant further argues that Cleland makes no reference to the encapsulation of bioactive substances or to the encapsulation where bioactivity of the substance is preserved. The examiner respectfully disagrees. First, the examiner points to column 6, lines 54-7 of the reference, which states "the term 'encapsulation' as used herein denotes a method for formulation an active agent such as an adjuvant or antigen into a composition useful for controlled release of the active agent. The examiner looks to Webster's Third New International Dictionary to define the words bioactive and antigen (see attached definitions). Bioactive means having an effect on a living organism. An antigen is a protein or carbohydrate substance that when introduced into the body stimulates the production of an antibody. Therefore, based on these definitions, an antigen clearly falls within the broad category of bioactive substances, as antigens clearly have an effect on living organisms.

Applicant further argues that Cleland does not teach any type of polymer microsphere other than PLGA microspheres. This argument is also found unpersuasive. The examiner points to column 6, lines 57-62, where Cleland teaches "examples of encapsulating material useful in the instant invention include polymers or copolymers of lactic and glycolic acids, or mictures of such polymer and/ or copolymers, commonly referred to as "polylactides" or "PLGA", although any polyester or other encapsulation material may be used." [Emphasis added]. First, this passage clarifies that Cleland does not limit the polymer to PLGA, but allows that other polymer

substances may be used. Second, the above rejected claims are drawn to polymers in general, and do not exclude the use of PLGA polymers.

For these reasons, the above rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 8-11, 15, and 17are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleland *et al.* in view of "Improving protein therapeutics with sustained release formulation" by Putney and Burke (Putney).

Cleland *et al.* are discussed above as disclosing a method of encapsulating peptides and proteins. Cleland *et al.* do not disclose the use of a stabilizer in their process of microencapsulation.

Putney discloses the importance of stabilizers in maintaining protein stability during encapsulation. Putney teaches that stability is necessary because the polymers used for encapsulation are not water soluble, and therefore essentially all microencapsulation processes required exposing the protein to nonaqueous solvents (p 154). Putney further teaches that several approaches can stabilize proteins during emulsion processes. One of these approaches is the inclusion of carrier proteins, such as albumin (p 155). Further, Putney teaches a related method is to maximize the therapeutic protein concentration in the encapsulated solution. Putney

teaches that another approach is to add small-molecule osmolytes such as mannitol or trehalose (p 155). Additionally, Putney teaches that a protein is better stabilized if it is encapsulated as a solid rather than in solution.

It is the position of the examiner that one of ordinary skill in the art would be motivated to improve the teachings of Cleland *et al.* using the teachings of Putney. Cleland *et al.* teaches the process of microencapsulation using polymers and polymer mixtures. Putney teaches that the process of microencapsulating proteins and peptides is greatly improved through stabilization techniques. Putney further gives several examples of successful stabilization processes. The expected result would be an improved microencapusulation technique. Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments have been considered but are not found to be persuasive. Applicant argues that Cleland in view of Putney does no more than state that it is obvious to try combinations of ingredients. The examiner respectfully disagrees. Cleland discusses the encapsulation of antigens. As discussed above, Webster's Dictionary defines an antigen as a protein which when introduced into the body stimulates the production of an antibody. Putney, discusses the importance of stabilizers in the encapsulation of proteins. Therefore, there is certainly motivation for combining the teachings of the two references. One of ordinary skill in the art would take the advice of Putney, which is to use stabilizers when encapsulating protein materials, and use this advice when practicing the invention of Cleland, which involves the encapsulation of proteins (antigens).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

For these reasons, the above rejection is maintained.

Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleland *et al.* in view of US Patent 5,560,438 to Collee *et al.*. Cleland *et al.* teach that more than one encapsulating material can be used in their invention, however, they do not go on to list possible encapsulating materials. Collee *et al.* is relied upon for the teaching that polyethylene glycol is a known encapsulating material (c 5, l 4).

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant argues that Collee is non analogous art. In response to applicant's argument that Collee is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, both references discuss encapsulation methods. As stated in the above rejection , Colle is relied

upon broadly to show that polyethylene glycol is a known encapsulation material. Therefore, the rejection is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E Pulliam whose telephone number is 703-308-4710. The examiner can normally be reached on Mon-Thurs 7:30-5:00, Alternate Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 703-308-2927. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

A. Pulliam
Patent Examiner
Art Unit 1615
October 16, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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